ACUTE TOXICITY SUMMARY

ARSENIC AND INORGANIC ARSENIC COMPOUNDS

Molecular formula	Molecular weight	Percent As by weight	Synonyms	CAS Registry Number
As	74.92	100%	arsenic black, metallic arsenic	7440-38-2
As_2O_3	197.82	75.7%	arsenious acid, crude arsenic, white arsenic	1327-53-3
$AsCl_3$	181.28	41.3%	arsenic butter, trichloroarsine, arsenious chloride	7784-34-1
As_2O_5	229.82	65.2%	arsenic anhydride, arsenic oxide, arsenic acid anhydride	1303-28-2
$AsH_3Na_2O_4$	185.91	40.3%	arsenic acid disodium salt, disodium arsenate, sodium arsenate dibasic	7778-43-0
$AsHNaO_2$	130.92	57.2%	arsenous acid disodium salt, arsenious acid sodium salt	7784-46-5

I. Acute Toxicity Summary (for a 4-hour exposure)

Inhalation reference exposure level	**0.19 µg As/m³**
Critical effect(s)	decreased fetal weight in mice
Hazard Index target(s)	Reproductive/developmental

II. Physical and Chemical Properties (For metallic arsenic except as noted) (HSDB, 1993 except as noted)

Description	yellow, black or gray solid
Density	As: 5.727 g/cm^3 @ 14°C $AsCl_3$: 2.16 g/cm^3 @ 25°C
Boiling point	613°C (sublimes) (ACGIH, 1991)
Melting point	sublimes (see boiling point)
Vapor pressure	760 mm Hg @ 372° C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in nitric acid, insoluble in water (salts and oxides are soluble in water)
Odor threshold	not applicable

Odor description	not applicable
Metabolites	dimethylarsinic acid, methylarsonic acid
Conversion factor	not applicable for As; $AsCl_3$: 1 ppm = 7.41 mg/m³

III. Major Uses or Sources

Arsenic is ubiquitous and is found in small amounts in soils and water throughout the world and also in foods, particularly seafood (NIOSH, 1976). Ore refining processes, including the smelting of copper and lead, are the major sources of release of arsenic dust and inorganic arsenic compounds. Arsenic trioxide is the form of inorganic arsenic most commonly produced. It is used as a raw material for the production of other inorganic arsenic compounds, alloys, and organic arsenic compounds (Kirk-Othmer, 1978).

Pesticides constitute the largest single use (50%) of arsenic compounds (HSDB, 1993). The major arsenic herbicides manufactured are monosodium methyl arsonate (MSMA), disodium methyl arsonate (DSMA), and dimethyl arsenic acid (cacodylic acid). Inorganic arsenic compounds are also used as herbicides (arsenite), insecticides (calcium and other arsenates), or rodenticides (sulfides) (ACGIH, 1991). Arsenic trichloride, for example, is used mainly as a chemical intermediate in the production of insecticides, but has other applications in the ceramics and pharmaceutical industries (HSDB, 1993). Arsenic is used as a pesticide to treat tobacco; thus, cigarette smoke is another common source of exposure (U.S.EPA, 1984).

Arsenic-based wood preservatives constitute the next largest use (40%) of arsenic compounds (HSDB, 1993). Arsenic pentoxide is used in the manufacturing of colored glass and as an insecticide and soil fumigant, but its major use is in formulated wood preservatives (HSDB, 1993).

The glass and electronic industries are also consumers of arsenic compounds. In the manufacture of semiconductors, elemental arsenic is alloyed with gallium and other heavy metals (HSDB, 1993). Several arsenic compounds are used in the production of colored glass.

The highly toxic trivalent arsenic compounds, such as arsenic trioxide, are typically introduced into the environment as a result of industrial processes including the smelting of metal ores. Pentavalent arsenic compounds are generally considered to be less toxic and are most frequently found naturally.

IV. Acute Toxicity to Humans

The relative toxicity of arsenic compounds decreases as follows: arsine(III) > organo-arsine derivatives > arsenites(III) > arsenoxides(III) > arsenates (V) > pentavalent organic compounds (V) > arsonium metals (I) > metallic arsenic (0), where the Roman numeral indicates the oxidation state (HSDB, 1993).

Acute inhalation exposure may result in severe irritation of the mucous membranes of the upper and lower respiratory tract with symptoms of cough, dyspnea, and chest pain (Friberg *et al*., 1986). These may be followed by garlicky breath and gastrointestinal symptoms including vomiting and diarrhea (HSDB, 1993). Signs of acute poisoning are dermatitis, nasal mucosal irritation, laryngitis, mild bronchitis, and conjunctivitis (Friberg *et al*., 1986). The acute toxic symptoms of trivalent arsenic poisoning are due to severe inflammation of the mucous membranes and increased permeability of the capillaries (HSDB, 1993). Inorganic arsenic compounds are easily absorbed through the skin; the trivalent is more rapidly absorbed than the pentavalent (Reprotext, 1999).

Ingestion of 2 g of As_2O_3 was fatal to an adult male (Levin-Scherz *et al*., 1987). Populations on the southern coast of Taiwan, chronically exposed to variable high concentrations of arsenic (0.10-1.81 ppm) in deep-well water used for drinking, exhibit an endemic peripheral vascular disorder named "blackfoot disease" (Yu *et al*., 1984). This condition results in gangrene of the extremities, especially the feet.

Predisposing Conditions for Arsenic Toxicity

Medical: Persons with skin or respiratory conditions, including allergies, may be more sensitive to the toxic effects of arsenic (HSDB, 1993).

Chemical: Persons with higher than normal intakes of arsenic, including smokers and fish and shellfish eaters, may be more sensitive to toxic effects following arsenic exposure (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

The LC_{Lo} for $AsCl_3$ in the cat for a 20 minute inhalation exposure is 100 ppm (740 mg/m³) (Flury, 1921). In the mouse, the LC_{Lo} of $AsCl_3$ for a 10 minute exposure is 338 ppm (2500 mg/m³) (Flury, 1931).

Mortality in mice challenged with aerosolized streptococci following a 3-hour exposure to 123-940 µg As/m³ (in an arsenic trioxide aerosol) increased in a dose-related manner with increasing concentrations of As_2O_3 (Aranyi *et al*., 1985). Pulmonary bactericidal activity (type unspecified) was significantly decreased in all mice exposed for a single 3-hour period to concentrations greater than 123 µg As/m³. No adverse effects were observed following a single 3-hour exposure to 123 µg As/m³.

A single intratracheal instillation of 17 mg As_2O_3/kg in rats resulted in multifocal interstitial pneumonia and focal proliferative bronchiolitis and alveolitis observed at necropsy 14 days post-exposure (Webb *et al*., 1986). The authors suggest (but do not confirm) that As_2O_3 induced an acute fibrogenic response.

VI. Reproductive or Developmental Toxicity

Arsenic is listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as a developmental toxicant. The oxidation state of arsenic determines the teratogenic potential of its inorganic compounds; trivalent (III) arsenic compounds possess greater teratogenic potential than pentavalent (V) compounds. In hamsters, a single maternal intravenous injection of 20 mg/kg sodium arsenate (V) ($AsH_3Na_2O_4$) on gestation day 8 was lethal to 44% of all embryos (Willhite and Ferm, 1984). A smaller dose (10 mg/kg) of sodium arsenite (III) ($AsHNaO_2$) administered in the same manner resulted in 90% embryonic lethality.

Fetal malformations, including exencephaly, resulted from an intravenous injection of $AsH_3Na_2O_4$ (V) into pregnant hamsters on gestation day eight (Ferm and Carpenter, 1968). The reproductive NOAEL in this experiment was 5 mg/kg. A significant reduction in fetal body weight, but no malformations were observed following a maternal dose of 5 mg/kg $AsHNaO_2$ (III) by the same route on gestation day eleven or twelve (Harrison and Hood, 1981).

A significant increase in pre-implantation mortality followed exposure of pregnant rats to aerosolized As_2O_3 at 1 mg/m³ for 5 months; no maternal toxicity was observed (Kamkin, 1982). At the LOAEL, 0.3 mg/m³, slightly elevated pre-implantation lethality was observed. The validity of this report cannot be evaluated, however, because key experimental details were not reported

Pregnant mice were exposed to 0.26, 2.9, or 28.5 mg/m³ As_2O_3 for four hours per day on days 9-12 of gestation (Nagymajtenyi *et al*., 1985). A significant dose-related decrease in fetal weight was observed in the offspring of exposed dams. Dose-related increases in hepatocellular chromosomal damage were observed in all exposed groups; in the highest dose group the chromosomal damage was statistically significantly different from the control. The percent of dead fetuses per dose group also increased in a dose-related manner. Maternal toxicity was not reported

A significant decrease in spermatozoa motility was observed in male rats following continuous exposure to As_2O_3 at a concentration of 40 mg/m³ for 48 hours (Kamil'dzhanov, 1982). Intravenous injection of radioactive arsenate (V) or arsenite (III) in several rodent species, including mice and hamsters, resulted in accumulation of arsenic in the lumen of the epididymal duct, which suggests that long term exposure of sperm may occur *in vivo* following acute exposure to As (Danielsson, 1984).

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Mild Adverse Effect Level

Because the most sensitive endpoint found in the literature was reproductive toxicity which is a potentially disabling, severe adverse effect, a discomfort or mild adverse effect level is not recommended.

Reference Exposure Level for a 4 hour exposure (protective against severe adverse effects):

0.19 µg As/m³

Because of the uncertainty of extrapolating from repeated dose studies to a one-hour concentration, for the reproductive endpoint we have chosen to use one-day's exposure regimen as a basis for the REL. Thus, for arsenic, this REL is for a 4-hour exposure.

Study	Nagymajtenyi *et al*., 1985
Study population	pregnant mice
Exposure method	maternal inhalation exposure for 4 hours on gestation days 9, 10, 11, and 12
Critical effects	decreased fetal weight
LOAEL	0.26 mg/m³ As_2O_3 (0.19 mg As/m³)
NOAEL	not determined in this study
Exposure duration	4 hours per day
LOAEL uncertainty factor	10
Interspecies uncertainty factor	10
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	1,000
Reference Exposure Level	0.00019 mg As/m³ (0.19 µg As/m³)

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH lists a revised IDLH of 5 mg/m³ on the NIOSH web site (http://www.cdc.gov/niosh), which is derived from an oral lethality study of calcium arsenate in dogs.

VIII. References

(ACGIH) American Conference of Governmental Industrial Hygienists. Documentation of Threshold Limit Values and Biological Exposure Indices. 6th ed. Cincinnati (OH): ACGIH; 1991. p. 82-84.

Aranyi C, Bradof JN, O'Shea W, Graham JA, Miller FJ. Effects of arsenic trioxide exposure on pulmonary antibacterial defenses in mice. J Toxicol Environ Health 1985;15:163-172.

Bauer RJ. Arsenic: glass industry requirements. In: Lederer WH, Fensterheim RJ, editors. Arsenic: Industrial, Biomedical, Environmental Perspectives. New York (NY): Van Nostrand Reinhold Co; 1983. p. 46.

Beaudoin AR. Teratogenicity of sodium arsenate in rats. Teratology 1974;10:153-158.

Danielsson BRG, Dencker L, Lindgren A, Tjalve H. Accumulation of toxic metals in male reproductive organs. Arch Toxicol Suppl 1984;7:177-180.

Diaz-Barriga F, Llamas E, Mejia JJ, Carrizales L, Santoyo ME, Vega-Vega L, Yanez L. Arsenic-cadmium interaction in rats. Toxicology 1990;64(2):191-203.

Dinman BD. Arsenic: chronic human intoxication. J Occup Med 1960;2:137-141.

Ferm VH, Carpenter SJ. Malformations induced by sodium arsenate. J Reprod Fertil 1968;17:199-201.

Flury F. Uber Kampfgasvergiftungen. IX. Lokal reizende Arsenverbindungen (in German). Zeichschrift fur die Gesamte Experimentelle Medizin 1921;13:527-528.

Flury F , Zernik F. Schadliche Gase - dampfe, nebel, rauch- und staubarten. Berlin, Germany: Verlag von Julius Springer; 1931. p. 180. [cited in Spector, 1956.]
.
Friberg L, Norberg GF, Vouk VB, editors. Handbook on the toxicology of metals. Vol. 2: Specific metals. 2nd ed. Amsterdam: Elsevier; 1986. p. 59.

Harrison WP, Hood RD. Prenatal effects following exposure of hamsters to sodium arsenite by oral or intraperitoneal routes [abstract]. Teratology 1981;23:40A [cited in Willhite and Ferm, 1984.]

(HSDB) Hazardous Substances Data Bank. National Library of Medicine, Bethesda, Maryland (CD-ROM Version). Denver (CO): Micromedex, Inc.; 1993. (Edition expires 11/31/93).

Hine CH, Pinto SS, Nelson KW. Medical problems associated with arsenic exposure. J Occup Med 1977;19(6):391-396.

Kamil'dzhanov AX. Hygienic basis for the maximum permissible concentration of the arsenic trioxide in the ambient air. Gig Sanit 1982;2:74-75.

Kamkin AB. For a revision of the maximum permissible concentration of arsenic trioxide in the ambient air of inhabited areas. Gig Sanit 1982;1:6-9

Kirk-Othmer Encyclopedia of chemical technology. Grayson M, executive editor. 3rd ed. Vol. 3. New York (NY): John Wiley and Son Publishers; 1978. p. 247-251.

Levin-Scherz JK, Patrick JD, Weber FH, Garabedian C. Acute arsenic ingestion. Ann Emerg Med 1987;16(6):702-705.

Merck Index. Windholz M, editor. 10th ed. Rahway (NJ): Merck and Co., Inc.; 1983

Nagymajtenyi L, Selypes A, Berencsi G. Chromosomal aberrations and fetotoxic effects of atmospheric arsenic exposure in mice. J Appl Toxicol 1985;5(2):61-63.

(NIOSH) National Institute for Occupational Safety and Health. CG17500. Arsenic chloride. In: Registry of toxic effects of chemical substances (RTECS) 1976 edition. Publication No. 76-191. Cincinnati (OH): US Department of Health, Education and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, DHEW (NIOSH); 1976. p.126.

NIOSH. Chemical listing and documentation of revised IDLH values (as of March 1, 1995). Available at http://www.cdc.gov/niosh/intridl4.html.

Pinto SS, McGill CM. Arsenic trioxide exposure in industry. Ind Med Surg 1953;22(7):281-287

Reprotext ® System. Dabney BJ, editor. Denver (CO): Micromedex, Inc.; 1999. (Edition expires 1/31/1999).

Spector WS, editor. Handbook of toxicology. Acute toxicities of solids, liquids and gases to laboratory animals. Philadelphia: WB Saunders Co; 1956. p. 324.

(U.S.EPA) United States Environmental Protection Agency. Health assessment document for inorganic arsenic. EPA-600/8-83-021F. Research Triangle Park (NC): US Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria Office; 1984. p. 2-5.

Watrous RM, McCaughey MB. Occupational exposure to arsenic in the manufacture of arsphenamine and related compounds. Ind Med 1945;14(8):639-646.

Webb DR, Wilson SE, Carter DE. Comparative pulmonary toxicity of gallium arsenide, gallium (III) oxide, or arsenic (III) oxide intratracheally instilled into rats. Toxicol Appl Pharmacol 1986;82:405-416.

Willhite CC, Ferm VH. Prenatal and developmental toxicology of arsenicals. In: Friedman M, editor. Nutritional and toxicological aspects of food safety. Vol. 9. New York: Plenum Publishing Corp; 1984. p. 205-228.

Yu S, Sheu H, Ko S, Chiang L, Chien C, Lin S, *et al*. Studies on blackfoot disease and chronic arsenism in southern Taiwan: With special reference to skin lesions and fluorescent substances. J Dermatol 1984;11:361-370.